Essential Interventional Cardiology

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Note
Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editors, authors, contributors and the publishers have taken care to ensure that the information given in this text is accurate and up to date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice.

Existing UK nomenclature is changing to the system of Recommended International Nonproprietary Names (rINNs). Until the UK names are no longer in use, these more familiar names are used in this book in preference to rINNs, details of which may be obtained from the British National Formulary.

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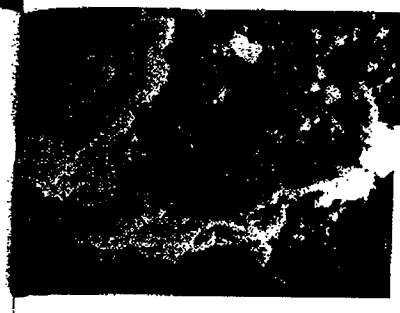


Intra-coronary stenting

E. JOHN PERRINS

KEY POINTS

- Stents are a landmark technology and are used in the majority of percutaneous interventions (PCI).
- Modern stents are both radially strong and conformable.
- Balloon expandable slotted tube stents predominate.
- Stents are available pre-mounted on balloons with a wide variety of diameters and lengths.
- Stents reduce restenosis and reintervention in PCI.
- Stents reduce acute complications of conventional balloon angioplasty and reduce the need for emergency bypass surgery.
- Bifurcations, long diffuse lesions and small vessels have higher restenosis rates.
- In-stent restenosis is difficult to treat.

The development and widespread use of coronary stents has probably been the single most significant advance in the field of interventional cardiology over the last 10 years. So much so that the use of a stent at the time of coronary artery dilatation is now carried out in more than 70% of all intra-coronary angioplasty procedures and so, in many ways, coronary angioplasty has become coronary stenting. Despite this coronary stenting is still perceived as a relatively immature technology; there is still very significant and important debate concerning its exact role and there is a proliferation of stent designs, stent technologies and stent coatings which continue to challenge the interventional cardiologist to try and utilise them to their best ability. The increased cost of stenting represents financial challenges that have been taken up to a greater or lesser extent in different health-care systems and countries. The UK, as in so many other things, tends to lag behind other developed countries in this regard.

The fundamental principle of coronary stenting is that a mechanical scaffold will be placed at the site of the treated segment of the coronary artery. The scaffold increases the radial strength of the vessel wall thereby preventing elastic recoil. In addition by pressing the intima firmly against the media of the arterial wall, it will tend to prevent disruption of the plaque or dissected flaps from proliferating or expanding and may cause more rapid healing at the site of the intervention. Equally the stent itself will introduce new properties into the treated segment of artery. It will

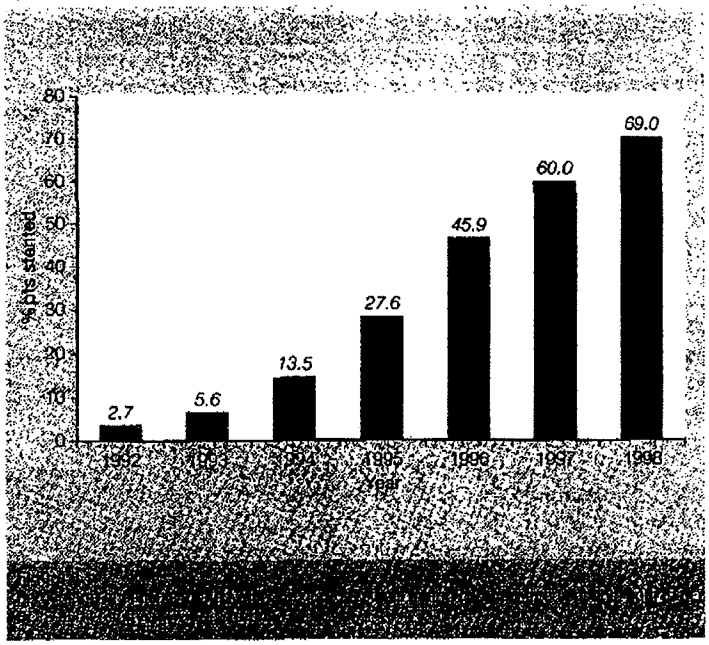
alter the fundamental elasticity of that vessel and the stent itself may induce subsequent biological changes, for example intimal hyperplasia, which may to some extent undo the initial advantages of placing the stent in the first place (restenosis).

Fundamental challenges in stenting

- The actual mechanical design of the stent itself.
- The problem of physically delivering the stent to the coronary artery in question.
- Expanding the stent to its proper dimensions.
- Ensuring that the stent is evenly and properly applied to the intimal surface of the vessel.
- The ensuing biological response to the stent itself.

The rapid growth of stenting in the UK is illustrated by Figure 6.1.

Although the widespread use of stents is a relatively recent phenomenon in the world of percutaneous coronary intervention (PCI) the concept of using a device to maintain the lumen goes right back to the originators of



angioplasty itself. Charles Dotter who originally described the use of progressive dilating devices to push through and create an opening in occluded peripheral vessels, also proposed in 1964 that a silastic supporting device might be placed in an artery following such a procedure to maintain patency.[1] Dotter and Judkins were also first to coin the term 'stent' to describe an intra-vascular implant in a peripheral artery in 1969. The origin of the word stent itself is obscure, but may be related to the work of a dentist, Charles Thomas Stent, who developed a material for taking dental impressions. In 1977 Grünzig made his first description of balloon coronary angioplasty, and the subsequent rapid interest and growth of that technique caused the concept of stenting to be put into the background. In 1983 Dotter and colleagues described the use of transcatheter placement of nitinol coil stents into canine arteries.[2] Shortly after, Maas and colleagues described the use of steel springs as a stenting device.[3] In 1985 Palmaz and colleagues hit upon the idea of using an angioplasty balloon to assist in the deployment of a stent in the peripheral arteries. They came up with the entirely novel concept of using a balloon to expand the stent within the coronary arteries; the technique that has now become more or less the de facto technique for intra-coronary stenting. In 1987 Palmaz and Schatz described the implantation of balloon expandable stents in the canine coronary circulation.[4] Between 1986 and 1988 a number of initial implantations of both balloon expandable and self-expanding (Wallstent) were reported in humans. All of the early stent experience was plagued by problems of thrombosis of the stent after placement, and the difficulty of manipulating relatively rigid and bulky stent devices into the appropriate part of the coronary circulation.

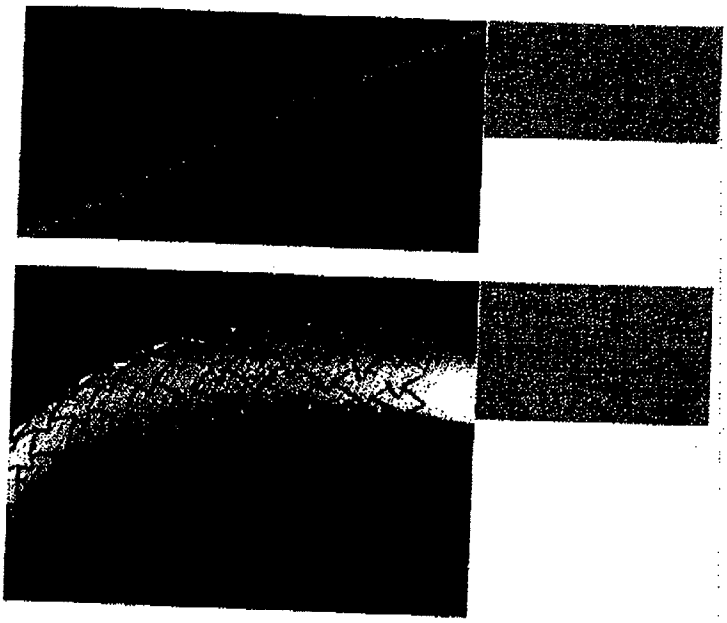
While these early attempts at developing coronary stent devices were taking place, it was apparent from the wider application of simple balloon angioplasty that this technique was not without its problems. In particular the problems of vessel dissection, acute closure and restenosis were starting to become a major limitation in the application of angioplasty. It was apparent to many of the pioneering investigators at that time that stenting might well provide a partial solution to all of these problems. In the early 1990s when the balloon expandable Palmaz–Schatz stent was the most practical and proven of the available devices, two seminal studies were commenced: the Benenstent in Europe and the Stress Study in North America.[5,6] These two randomised controlled studies focused on the use of coronary stenting in the single discrete lesion and looked specifically at restenosis rates compared with simple balloon angioplasty. Both studies showed a very important reduction in restenosis (Benenstent: 22% stent, 32% balloon. Stress: 32% stent, 42% balloon.) These trials although they have been extensively analysed and criticised, triggered an explosion in stenting which has continued unabated.

There have, of course, been numerous highly significant developments since Benestent and Stress were published. Antonio Colombo[7] is widely

regarded as having recognised that one of the fundamental problems with stent placement (particularly with the Palmaz–Schatz stent) was failure to completely expand all of the stent when placed in the coronary vessel. He proposed the technique of high pressure stent deployment, initially with the thought of over-expanding the stent, but subsequently realising, particularly with ultrasound, that the stents simply required a high pressure to completely expand them.

Although many stents are now manufactured claiming to require lower deployment pressures, most operators still deploy stents with pressures in the region of 10–16 atmospheres in the deploying balloon. The recognition that antiplatelet agents reduce subacute stent thrombosis, in particular the early use of ticlopidine, further opened the way to widespread stent usage. Controlled trials[8] showing that warfarin actually added nothing and possibly increased complications in elective stenting allowed the abandonment of warfarin with marked reduction in femoral arterial closure complications. Of course the subsequent development of closure devices has largely eliminated these problems. Intravascular ultrasound has allowed us to fully appreciate the difficulties of actually estimating the proper diameter of the intra-coronary vessel, the adequacy of deployed stent expansion and the importance of covering all of the at risk lesion. Most significant of all has been the technological development carried out by the stent manufacturers in producing balloon expandable stents that have a low profile, high flexibility and which are easy to use.

Most articles on coronary stenting describe the various stent designs available at the time of writing the book or chapter. In my view all this does is uniquely date the text as stent design and development is progressing so rapidly that even in the relatively short time it has taken to produce this book any such information may be out of date. However, it is fair to say that the balloon expandable stent currently reigns supreme and as nearly all of the balloon expandable stents share common design features I will concentrate on these. Julio Palmaz had the brilliant idea that if one took a very thin stainless steel tube and cut small longitudinal slots in that tube using a laser cutter, if the tube was then expanded by a balloon then the expanded slotted tube would become a mesh. Clearly the shape and properties of that mesh would depend entirely upon the way the tube was cut, the material from which the tube was made and the way in which the tube was expanded with the balloon. As with so many good ideas, he initially found it difficult to interest a manufacturer to produce it. Johnson & Johnson Inc. (who had had very little prior involvement with cardiac intervention) eventually listened to his suggestions and the balloon expandable stent was born. Figure 6.2 shows the appearance of a modern balloon mounted slotted tube stent in expanded and unexpanded forms.



Desirable design features for stents

- Biologically inert
- Flexible when mounted on delivery balloon
- Good radio-opacity
- Radial strength and conformable when expanded
- Smooth surface and/or coating
- Good side branch access through stent cells
- Availability of wide range of diameters and lengths
- Reduced metal or cell design for smaller vessels, increased for larger diameter vessels
- Low cost.

The design of any stent is always a trade-off between a number of desirable characteristics. The stent requires radial strength in order to prevent the collapse of the stent and to hold the wall of the stented segment of artery firmly in place. However, at the same time the stent needs to be conformable and flexible, both when it is compressed upon the delivery balloon and when it is expanded within the coronary vessel,

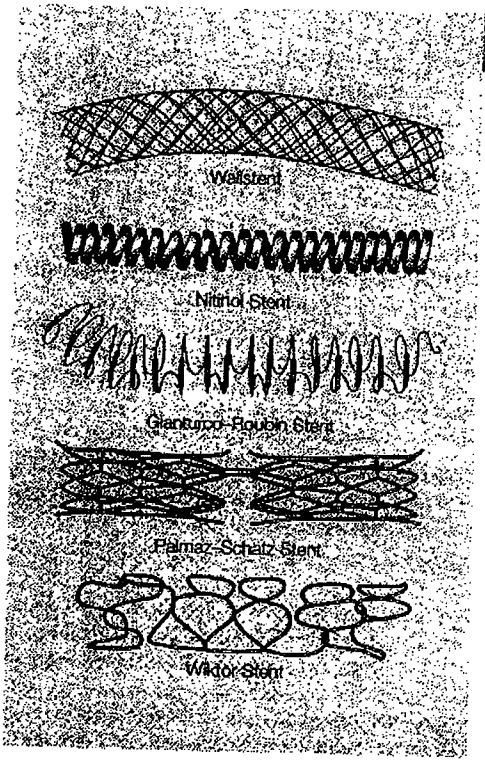
since coronary vessels have highly complex 3D shapes. The material of the stent must be biologically inert. It is a highly desirable characteristic that the stent can be seen during its placement, by utilising X-ray screening equipment. The radio-opaqueness of the stent is therefore a vital factor when actually implanting it. The surface of the stent needs to be smooth, in order to attract as little platelet attachment as possible. In early stent designs, because of the problems of the rigidity of the slotted tube, small segments of slotted tube were linked together by articulations. This allowed the stent to bend in certain places but obviously meant that the coverage of the wall of the vessel would be incomplete at the point of articulation. Numerous clever geometric designs in the method of cutting the stainless steel tube have now resulted in stents that are both flexible, but have radial strength. The size of the associated cells in the expanded mesh is therefore not too large. Many manufacturers now produce different stents for different sizes of vessel, providing different diameters. Obviously if one stent is used for all coronary diameters, then the larger the stent is expanded the smaller the amount of vessel wall that will be covered. The stent may therefore have too much metal coverage in small vessels and too little in large vessels. Most stents are made from some form of stainless steel, although other metals have been used, particularly nitinol and tantalum. Stents have also been coated in a range of various materials, most of which have a neutral effect, although there has been some suspicion that coating the stent with gold may produce adverse consequences. More recently attention has focused on other methods of coating a stent, for example the PC coating process (Biocompatibles Inc.) and the Carmeda coating process – bonding heparin to the surface of the stent (Cordis Inc.). Obviously modifying the surface properties of the stent may eventually allow lower platelet activation and reduce the amount of intimal hyperplasia, but there is no real clinical evidence to support this. In the early days of stenting, the stent was supplied on its own and had to be crimped, usually by hand, on to an angioplasty balloon. Modern stents almost invariably consist of a stent pre-mounted on the balloon, and in fact balloons are now designed specifically to accept stents. Many stents are heat-sealed on to the balloon, so that it is almost impossible to detach the stent while the balloon is deflated.

There are many other stent designs (Fig. 6.3). Some have used coiled or twisted wire to produce expandable cells which can then be welded together to form longer stents (e.g. AVE Micro stent and GFX stents) Some are made entirely from complex coils which when expanded are similar to mesh stents (Cordis Crossflex). Others have used a steel backbone to which are attached segments which can be expanded. Finally there was the Wallstent, a lattice work of stainless steel wires which when unconstrained expand to form a tube. The device is held in its collapsed state by a sheath which when withdrawn allows the stent to self-expand. Although still used in larger peripheral vessels, the wallstent is rarely used in the coronary circulation today.

Covered stents

All the stents discussed so far are various kinds of meshes which have holes in them. Covered stents aim to totally cover the intimal surface of the treated vessel in a manner similar to a tube graft. The only current device is the Jomed covered stent which consists of a thin tube of polythene sandwiched between two conventional slotted tube stents. As the stent is expanded the polythene stretches and forms a tube graft. There is uncertainty as to whether the covered stents will offer advantages over conventional stents; they are more difficult to deploy and expand due to their thickness. They do have a unique place however in the treatment of coronary perforation and in the exclusion of coronary aneurysms.

The technique of stent deployment is relatively simple in theory! Following conventional arterial access ordinary guiding catheters are used and a guidewire, usually 0.14, is used to cross the target lesion. Until relatively recently pre-dilatation of the target lesion was always required

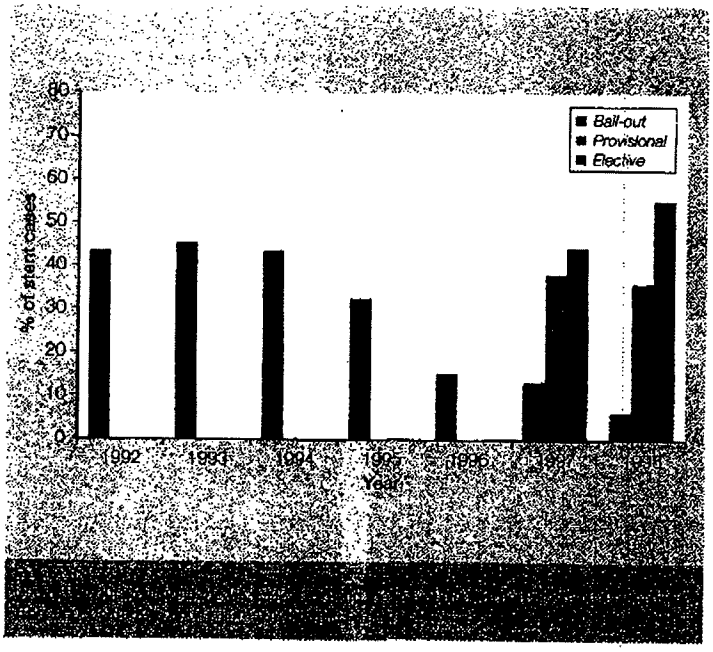


as the stent was too bulky to pass directly across the narrow vessel. However, in the last 2–3 years balloon mounted stents have become significantly lower in profile and have increased flexibility to allow direct crossing of the undilated lesion in a high proportion of cases, so called primary or direct stenting. Once the stent is positioned satisfactorily the balloon is inflated and generally the stent deployed at a pressure somewhere in the region of 10–16 atmospheres. Most modern stent deployment balloons allow a high enough pressure to be used so that the deploying balloon can carry out the final deployment of the stent. In addition stents are now mounted on balloons whose length is matched to that of the stent, removing the risk of either end of the deploying balloon damaging the unstented vessel wall when expanded to high pressure. However, for many reasons post-inflation of the stent may sometimes be required, often with a shorter balloon at even higher pressures. The wire is then withdrawn, the groin closed and the patient generally discharged the following day. Periprocedural heparin is generally considered to be essential; most centres will monitor KCT although this is not always universal, and with the use of or increasing use of GPIIb/IIIa inhibitors such as Reo-Pro, weight-adjusted heparin is more commonly used. Powerful antiplatelet drugs such as ticlopidine or more recently clopidogrel are universally prescribed following stent deployment. Some centres will only use aspirin, particularly in larger stented segments, but the majority of centres, particularly in the UK, will use aspirin and clopidogrel. There is no absolute agreement either on the duration of treatment required with antiplatelet drugs or on the doses, but the use of 75 mg clopidogrel and 300 mg aspirin for at least 2 weeks and often 4 weeks following the procedure is common, and most patients will be maintained on aspirin at lower doses indefinitely unless they are hypersensitive to it. Warfarin is generally not used in the context of coronary stenting nowadays. Several controlled trials suggested that it may actually increase the rate of complication, but in patients who are already established on warfarin for some other reason, then the operator has to take in individual patient considerations as to whether to continue warfarin during the first few weeks of the procedure.

The clinical selection of patients for intervention is covered elsewhere in this book. Stents are placed in the following situations:

- Bail-out
- Elective with pre-dilatation
- Elective without pre-dilatation.
- Following a preceding device therapy (e.g. after rotablator).

In the early days of stenting stent placement for bail-out indications after unsatisfactory or unsuccessful balloon angioplasty or other device



intervention was the primary indication. However following the realisation that elective stenting reduced restenosis, bail-out stenting is now uncommon (Fig. 6.4). There is still discussion as to whether provisional stenting should be carried out. However particularly with primary stenting (see below) it is unquestionably quicker and cheaper to perform primary stenting electively rather than provisional stenting (i.e. balloon angioplasty first and only stent if angiographic result is unsatisfactory).

Figure 6.5a–e illustrates a primary stent procedure using only one balloon mounted stent and no additional balloons or other devices.

Procedural complications primarily relate to whether it is possible to deliver a stent to the intended site in the coronary artery. As operators started to use stenting in more complex coronary arteries, the limitations of the mechanical properties of the stent–balloon combination sometimes led to the situation where the unexpanded stent could not be taken forward to the desired place, requiring an attempt at withdrawing the stent balloon or deploying the stent in an unwanted area. Withdrawal of the undeployed stent on the balloon used to represent a considerable risk of the stent being pulled off the balloon and being left unexpanded, but

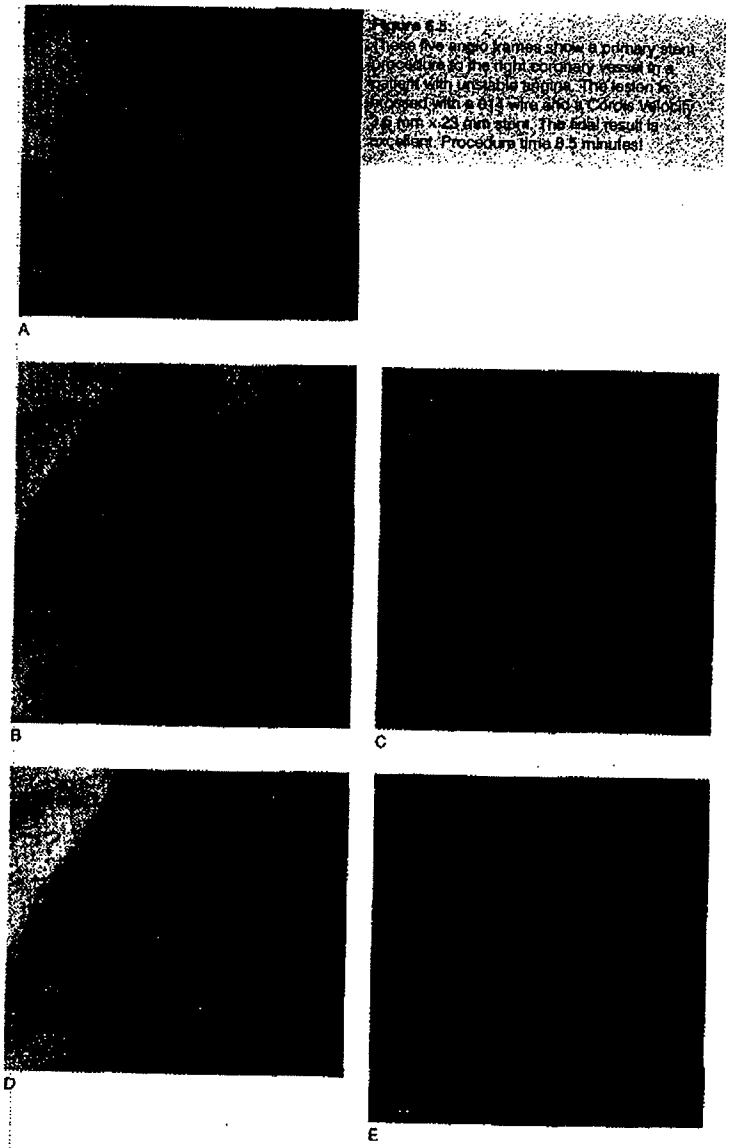


Figure 6.5
These five angio frames show a primary stent procedure in the right coronary vessel in a patient with unstable angina. The lesion is crossed with a 0.9 wire and a Cordis Velocity 3.0 mm × 23 mm stent. The final result is excellent. Procedure time 8.5 minutes.

left within the coronary circulation. This is now a very rare complication as most stents, if they have been applied to the balloon by the manufacturer, are very resistant to being loosened in this way. However, there are many operator errors which can still allow this to occur, for example if the balloon has been inflated at any time during the procedure, the stent may have been loosened. If the balloon is left on negative pressure during deployment (the routine for balloon angioplasty) the balloon may loosen from the stent sufficiently for it to come off the balloon. Occasionally when a stent is withdrawn back into a guiding catheter, the edge of the catheter will lift up the back of the stent and then strip it off the balloon as the balloon is withdrawn. The importance of screening the balloon and stent whenever the balloon and stent are moved together cannot be emphasised enough but particularly during withdrawal. It is vital to ensure that the tip of the guide catheter and the stent are as coaxial as possible during withdrawal. Even when the stent balloon is not being intentionally withdrawn it may move between the time at which the stent was in the right position and the time at which the balloon is actually inflated. It is very important to continue to screen at the time of the inflation.

Under-expansion of the stent

The second major group of procedural complications relate to inability or failure to deploy the stent adequately, even though it may be in the right place. Routine use of relatively high pressure balloon expansion together with more compliant stent designs have made this complication less common, but adequate expansion of the stent is fundamentally predicated by having selected a stent of the correct diameter for the lumen of the vessel. Also, the routine use of quantitative coronary angiography (QCA) is still to be highly recommended to ensure proper selection of stent size as long as it is carried out and calibrated properly. Strict attention to the appearance of the stent following deployment in more than one projection remains vital to assessing whether the stent is actually deployed both completely and at the right diameter. As mentioned earlier in this chapter under-deployment of the stent is one of the fundamental causes of subacute stent thrombosis and unquestionably contributes to a higher restenosis rate.

Edge dissections

Stenting fundamentally reduces the risk of dissection at the point at which the stent is placed. However, sometimes a dissection will propagate from the end of the stent. Most commonly this is a distal edge dissection. If there is only a very small shelf or irregularity at the end of the stent then it may not be necessary to do anything further, but it is very important to observe the lesion for a minute or two if nothing else is done. However, in the author's experience one commonly ends up having to place another stent at the outflow of the first. Although intravascular ultrasound is well

described as a way of helping to manage these kinds of complication, the fact that it is not used routinely generally leads operators to place another stent. Anterograde dissection is much less common but potentially very serious, because if a dissection propagates proximally towards the ostium of the stented vessel there is the risk of involvement of the main stem or another major proximal side branch. It is easy for the operator to miss proximal problems related to the stent. It should also be remembered that it is possible to dissect the proximal vessel during the passage of a stent, particularly if that stent passage has been difficult. Prompt stenting of the affected proximal segment of the vessel is essential and may be life saving. Proximal dissections can sometimes involve the wall of the aorta itself.

Side branches

Obviously whenever a stent is placed over the ostium of a side branch unpredictable consequences may occur. If the side branches are relatively small and there is clearly good angiographic flow down the side branch, then experience has shown that no further attention to that side branch is required. However, often a side branch may appear nipped or may even disappear when a stent is expanded across it. Most modern stents will allow the passage of a wire through the mesh into a side branch which can then generally be dilated and even stented itself. As soon as the operator moves into that realm he has to face up to the techniques and limitations of bifurcation stenting which will be discussed in a later section.

Vessel rupture

Vessel rupture during stenting itself is relatively rare although obviously it may occur, particularly during pre-dilatation. Occasionally if a lesion is resistant to dilatation and very high pressure is required, a balloon rupture may still cause a vessel perforation despite a stent having been placed. Stenting may, of course, be a life saving manœuvre when vessel rupture has occurred for other reasons and the covered stent is particularly useful in that rare but very dramatic situation. Inflation of a standard angioplasty balloon in the vessel proximal to the perforation will often prevent major bleeding into the pericardium.

Distal embolisation

Significant embolisation of material following a stent expansion in a stable chronic atheromatous plaque is very rare. However, as stenting is used more and more both in acute unstable syndromes and in myocardial infarction, stents are increasingly being used in situations where embolisation may occur. It is the author's personal experience that in this situation primary or direct stenting comes into its own as the balloon and stent can be placed directly across a soft friable lesion and the stent expanded and deployed with a single balloon dilatation. Embolisation often occurs if post-dilatation of such a stent is then attempted. It is the author's opinion that post-dilatation should not be carried out on stents in

these acute and friable lesions. This is particularly important in the context of acute myocardial infarction or where stents are being placed in bulky friable vein grafts. The management of embolisation is difficult, and Reo-Pro would generally be considered to be mandatory unless there were some fundamental contraindication to its use. Intra-coronary nitrates and particularly intra-coronary verapamil may help to combat the no reflow situation that occurs. More recently devices are becoming available which may catch embolic material in particular high-risk situations (e.g. Cordis Angioguard).

By far away the most important complication in the early days of stenting was subacute stent thrombosis with abrupt closure of the vessel, usually within the first 7–14 days of stent placement. Modern antiplatelet treatment, high pressure ballooning and adequate stent to vessel sizing have largely eliminated this problem; in modern practice subacute stent thrombosis rates are well below 1%. Paradoxically it is now so rare that it may be missed altogether if a patient re-presents. Curiously if a subacute stent thrombosis does occur, simple ballooning of the stent together with heparin or Reo-Pro generally results in an excellent angiographic appearance and repeated subacute thrombosis seems to be virtually non-existent. Presumably it all relates to the mechanics of the initial stent dilatation.

Restenosis

Restenosis remains a fundamental complication of any percutaneous intervention and although stenting fundamentally reduces restenosis, it does not by any stretch of the imagination eliminate it. It is difficult to get a true perspective as to what the clinical impact of restenosis is. It is well known that angiographic restenosis rates are higher than clinical restenosis rates – a consistent feature in nearly all interventional trials. Clearly there is a fundamental difference between a restenosis and representation following interventional procedure. Within the UK at least restenosis appears to be being treated in between 7–10% of patients. The treatment of restenosis is a complex topic and in my view fundamentally relates to the context in which the original intervention was done, in particular whether additional moderate or perhaps more severe disease is still present in other vessels. Coronary artery bypass grafting is an excellent treatment for restenosis and it is essential that patients are offered surgical revascularisation if it is clearly the most appropriate option. All known methods of treating restenosis themselves result in a higher rate of further restenosis. In the author's view diffuse disease in long stents should always been treated by surgery unless there is a contraindication. Focal restenosis may well be susceptible either to balloon inflation, cutting balloon inflation or restenting. Because the material within the stent in a restenotic lesion is smooth and rubbery it is

often the case that if a balloon is inflated within a restenosed stent the balloon prolapses either antero-gradely or distally and does not expand the material. Repeated attempts to expand the stent in this situation can lead to catastrophic damage to the vessel; if migration of the balloon is occurring prompt restenting is the treatment of choice as the stent is able to engage the intimable hyperplasia and can then be deployed without migration of the balloon. Similarly the blades in the cutting balloon will cut into the intimal hyperplasia, generally allowing dilatation of the segment without balloon migration. Unfortunately it may be difficult to place the cutting balloon in the stented segment due to its rigidity and it may be difficult to obtain a good match of the length of cutting balloon to the length of restenotic segment. There has been a lot of focus on the use of radiation both for the treatment of restenosis and for its prevention and this is covered elsewhere in this book.

Small vessels

All of the randomised trials of stenting vs balloon angioplasty have shown a fundamental relationship between vessel size and restenosis. As vessel size gets smaller restenosis becomes more common. These data relate to stents which have not specifically been designed for small vessels. Newer designs allowing less wall coverage and with improved surface coatings may allow small vessel stenting with similar results to larger vessels, but clinical trial results are not yet available. Small vessel stenting probably relates to the use of stents in vessels between 2.25 and 2.75 mm internal diameter. Whether any intervention at all is justified in vessels smaller than 2 mm is not known.

At the moment it is hard to justify the use of stents in an elective scenario for small vessels. However, because small vessels are frequently involved in interventional procedures and are certainly no less likely to suffer complications of dissection than larger vessels it is often necessary to stent smaller vessels. It is important to attain the largest possible lumen size in these situations and the availability of quarter sized balloons, particularly 2.75 mm balloons, is important but not always recognised.

Left main stem

The left main stem used to be an absolute contraindication to angioplasty or stenting and although in general terms surgery should always be offered, there are many circumstances where surgery may be high-risk or impossible. There have been a number of studies presented of elective stenting in the left main stem scenario, particularly in elderly patients, and although these appear to be successful the short-term data suggest a considerably higher mortality in the region of 5–8%. One or two series have produced much better results, and it is likely that left main stem disease will be eventually treated by stents, particularly when there is a

discrete lesion not involving the bifurcation. However at the time of writing there is currently no acceptable indication for elective stenting of the left main stem other than where surgery is impossible or inappropriate.

Saphenous bypass grafts

The management of the diseased bypass graft is a difficult problem for everybody treating patients who have been revascularised. The graft is frequently diffusely diseased, may have friable material within it and often is of large diameter which may stretch the mechanical properties of stents to their limits. It should be remembered that nearly all of the longitudinal studies of stenting and angioplasty in vein grafts show a consistently higher restenosis rate, and perhaps much more importantly, a very significant chronic occlusion rate in the graft within 2 years of the procedure. With current technologies, stenting of a bypass graft cannot really be considered to be a definitive treatment. Careful attention should always be paid to the native vessels, because if it is possible to revascularise the native vessel to which the graft is attached, this is generally a better procedure to carry out and is likely to have a better long-term outcome. There is no convincing evidence that the use of ReoPro reduces the risk of complications from graft angioplasty other than where thrombus is clearly present. The newer thrombus collecting devices (Angioguard) although interesting are not yet proven. I believe primary stenting offers a fundamental advantage in the treatment of the bypass graft since by avoiding pre-dilatation and then placing the stent with one inflation, the risk of embolisation seems to be reduced. Therefore, primary stenting should be employed wherever possible in the saphenous vein graft.

Ostial lesions

Treatment of ostial lesions either of grafts or the right coronary artery is made simpler by stenting but the restenosis rates are significantly higher than in the body of the vessel. It can be very difficult to accurately size the ostium without intravascular ultrasound. Placement of the stent right up to the ostium can be difficult and careful guide catheter selection and positioning is required. It is very easy to miss the first 2–3 mm of the vessel with subsequent restenosis. The use of a longer stent (18 mm or greater) even in short discrete ostial lesions may be helpful as it allows easier positioning and decreases the chance of the stent moving during deployment. High pressures are required in the ostium but dissection of the main aortic wall is possible.

Bifurcation lesions

The treatment of coronary bifurcations remains the most technically challenging and contentious area of intervention. All current routine treatments have higher restenosis and adverse event rates than for lesions

in the body of the vessel. This applies as much to stenting as to other device technologies discussed elsewhere in this book. Coronary bifurcations are a heterogeneous collection of anatomical variations and different strategies are employed according to whether both limbs are involved, the angulation the proximal segment, etc. The presence of significant bifurcation disease, particularly at the left anterior descending (LAD)/diagonal position, mandates a careful consideration of the benefits of coronary artery bypass grafting. If other adverse factors such as diabetes are present then surgery has to be the strategy of first choice. A detailed discussion of bifurcation stenting is beyond the scope of this chapter.

- There is a steep learning curve.
- The use of two guidewires and simultaneous inflation of both pre-dilating and post-deployment balloons is associated with improved results.
- Primary stenting is currently not possible.
- Larger lumen guide catheters are helpful.
- Stent the most important (generally larger) vessel first.
- Culotte stenting (where both stents are in the proximal segment as well as in each limb) as widely advocated but early clinical results are uncertain.
- Wrapping of the two guidewires either in the guide catheter or in the proximal vessel can produce catastrophic 'jamming' of the two balloons or stents.
- A bifurcation restenosis is even more difficult to treat than the original lesion.

Long lesions

Stents are now generally available in a variety of lengths up to 40 mm. Longer lesions may require more aggressive pre-dilatation and the use of support wires may facilitate stent passage. Longer stented segments are probably associated with higher rates of in-stent restenosis. Very careful attention needs to be paid to adequate stent expansion. Post-dilatation to high pressure is more commonly needed and it is vital to taper the stent if the reference diameter at the start of the lesion is more than 0.5 mm of the distal lesion. Calcified long lesions are particularly likely to have some areas of poor stent expansion. Ideally intravascular ultrasound should be used in this situation to optimise deployment.

Stents have been shown to improve outcomes, not only when treating patients with stable angina, but also when treating unstable coronary syndromes, acute myocardial infarction and shock. Stents can now be placed very quickly, often without pre-dilatation. The reduction of

ischaemia during the procedure and the certainty that the vessel will remain open after the stent is placed dominate the acute clinical procedure. Stents should be used in all acute procedures with vessel size 2.5 mm or greater. There is considerable evidence that Reo-Pro (abciximab) is indicated prior to acute interventions for unstable angina. It produces both early and late mortality benefits, particularly in high-risk cases and diabetics. Trials in acute MI show an additional benefit to stenting compared to balloon alone and GP2a3b inhibitors add further benefit.

Stenting will continue to dominate PCI for some years to come. It is likely that primary or direct stenting will increase and formal clinical trials are under way. New aggressive stent coating technologies will probably be shown to have advantages, particularly in smaller vessels. There is still very active research into the area of bioabsorbable stents; they may ultimately be an even better method of local drug delivery than coated stents. Innovative devices will eventually allow better treatment of bifurcation and main stem disease. Restenosis will remain a clinical and technological challenge.

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New Stent Is Hailed in Cardiac Treatment

Published: Wednesday, September 5, 2001

A metal tube that opens clogged arteries and keeps them clear by releasing medication was hailed by doctors today as a potential breakthrough in fighting heart disease.

Johnson & Johnson, which developed the stent and sponsored the study, said it expected the device to be available in Europe next year and in the United States in 2003. The company's shares rose $3.44 in trading today, or 6.5 percent, to $56.15.

Some experts predict that the device, an improved version of the conventional stents already used to keep arteries open, will eliminate the need for repeat angioplasties and could spare some patients the trauma, risk and prolonged recovery associated with heart-bypass surgery.

A study of 238 patients in Europe and Latin America, presented here today at a meeting of the European Society of Cardiology, found that while arteries closed up again in 26 percent of patients implanted with a regular stent, there was no narrowing in any patient who received the drug-coated device. Also, 97 percent of the patients treated with the new stent, called Cypher, had no further heart trouble in the next six months, compared with 73 percent of the others.

The study's lead investigator, Dr. Marie-Claude Morice, head of interventional cardiology at the Jacques Cartier Hospital Institute in Massy, France, said, "We are probably witnessing a new era in the treatment of coronary disease."

Some others expressed caution. "You're still dealing with a systemic disease," said Dr. Karl Karsch, chief of cardiology at Bristol University in England. "Atherosclerosis is all over the body. You are just interfering at a lesion; you are not interfering with the disease."

A version of this article appeared in print on Wednesday, September 5, 2001, on section C page 15 of the New York edition.

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Effects of Diltiazem on Complications and Restenosis After Coronary Angioplasty

James H. O'Keefe, Jr., MD, Lee V. Giorgi, MD, Geoffrey O. Hartzler, MD, Thomas H. Good, MD, Robert W. Ligon, MA, Deborah L. Webb, RN, and Ben D. McCallister, MD

A randomized, placebo-controlled, double-blinded trial was performed to evaluate the usefulness of empiric therapy with a calcium antagonist in patients who undergo coronary angioplasty. A total of 201 patients were randomized to placebo or to high-dose diltiazem (mean dose, 329 mg/day). Treatment began 24 hours before angioplasty. Restenosis was assessed by percent area stenosis as determined by quantitative angiographic techniques before, immediately and 1 year after angioplasty. All patients also received aspirin and dipyridamole before angioplasty. Heparin and verapamil were administered intravenously during the procedure. The 2 groups were similar with respect to age, extent of coronary artery disease, smoking history, and baseline lipid levels. Procedural complications, including death (1 vs 1), Q-wave infarction (0 vs 3), acute occlusion (5 vs 5) and focal spasm (0 vs 0), were not significantly different in the diltiazem and placebo patients, respectively. Freedom from all acute complications was noted in 85% of patients in both groups. One-year angiographic follow-up was obtained in 60% of patients. Restenosis rates were similar: 36% in the diltiazem group and 32% in the placebo group (p = 0.30). The incidence of late cardiac events (death, Q-wave myocardial infarction, recurrent angina or coronary bypass graft surgery) was similar in the 2 groups. Thus, diltiazem did not influence the overall restenosis rate or prevent late events after coronary angioplasty.

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Calcium antagonists are theoretically attractive agents for use after coronary angioplasty. By reducing smooth muscle contraction at the angioplasty site, calcium antagonists might minimize ongoing endothelial trauma and platelet deposition in the early hours after the procedure. Vasospasm at the site of angioplasty during follow-up,[1] and elastic recoil[2,3] of the dilated segment, have also been implicated as causes of chronic restenosis. Calcium antagonists have been shown to retard the development of atherosclerosis in animal models,[4–8] and preliminary evidence suggests that this class of drugs may inhibit the development of new atherosclerotic lesions in humans as well.[9,10] Diltiazem and verapamil have mild antiplatelet activity,[11–13] and all calcium antagonists have been shown to provide cardioprotection during and after ischemia.[14–16] Thus, although there are many potential reasons for the empiric use of calcium antagonists in patients undergoing coronary angioplasty, clinical data on the actual conferred benefits are less well documented.[17] The purpose of the current study was to evaluate the usefulness of diltiazem in preventing acute complications, restenosis and recurrent cardiac events after elective coronary angioplasty.

METHODS

A total of 201 patients were enrolled in this randomized, placebo-controlled, double-blinded trial evaluating oral diltiazem for the prevention of restenosis after coronary angioplasty. Patients were excluded from study participation for angioplasty performed for an evolving acute myocardial infarction, high-grade atrioventricular block, sick-sinus syndrome, recent thrombolytic administration, or other severe concomitant medical illnesses. Both diltiazem and placebo were given on a 3 times per day dosing schedule. The diltiazem dose ranged from 240 to 360 mg per day (mean, 329 mg). Treatment began 24 hours before angioplasty. All patients received at least 1 dose before the procedure. Compliance monitoring revealed that 96% of all dispensed pills were ingested.

Angioplasty protocol Elective coronary angioplasty was performed using our standard protocol.[18] In this regimen, patients are pretreated for at least 24 hours with 325 mg of aspirin daily and dipyridamole 75 mg 3 times a day. The patients were routinely pretreated with 5 mg of intravenous verapamil, 75 mg of intravenous lidocaine, 5 mg of sublingual isosorbide dinitrate, 50 mg of dextran, and 10,000 units of intravenous heparin. A repeat heparin bolus of 5,000 units was given intrave-

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TABLE I Demographic Characteristics

	Treatment		
	Diltiazem (n = 102)	Placebo (n = 99)	p Value
Female/male (%)	14/88 (13.7/86.3)	18/81 (18.2/81.9)	0.44
Family history of heart disease (%)	54 (52.9)	52 (52.5)	1.00
Diabetes mellitus (%)	6 (5.9)	9 (9.1)	1.00
Cigarette smoking (%)	73 (71.6)	79 (79.8)	0.43
Total cholesterol >240 mg/dl (%)	13 (12.7)	15 (15.2)	0.19
Blood pressure >145/90 mm Hg (%)	42 (41.2)	35 (35.4)	0.69
Chronic lung disease (%)	4 (3.9)	3 (3.0)	1.00
Peripheral vascular disease (%)	3 (2.9)	3 (3.0)	1.00

nously at hourly intervals during the procedure. Immediately after angioplasty, a continuous intravenous heparin infusion was initiated for approximately 24 hours. During follow-up, other cardiac medications were used as needed; calcium antagonists and β-blocking drugs were avoided. Patients were contacted by telephone or office visits, or both, at 2, 4, 6, 9 and 12 months after angioplasty.

Quantitative angiography: Coronary stenoses were measured by quantitative angiographic techniques. The quantitative measurement was based on computer-assisted vessel and lesion reconstruction in 2 orthogonal views (Figures 1 and 2). This technique corrects for x-ray beam divergence and pin-cushion distortion and allows for accurate, absolute stenosis measurements, as well as a percent area stenosis calculation. Restenosis was defined as return to ≥70% or luminal area stenosis and loss ≥50% of the initial gain with angioplasty. Percent area stenosis and absolute minimal luminal diameter were also evaluated as continuous variables. In this model, restenosis is defined as the change in the mean from immediately after angioplasty to follow-up.

RESULTS

Randomization resulted in 102 patients in the diltiazem and 99 patients in the placebo groups. The 2 groups were similar with respect to demographic and baseline angiographic characteristics (Table I). In-hospital complications were similar in the 2 groups (Table II). Acute reocclusion occurred in 5% of both groups. An insignificant trend toward a lower incidence of procedure-related Q-wave myocardial infarction was noted in the diltiazem group.

Complete angiographic follow-up was available in 120 patients (60%). A single lesion was dilated in 63 patients, and 57 patients underwent multilesion percutaneous transluminal coronary angioplasty. Quantitative analysis showed a decrease in the mean area stenosis from 85% before percutaneous transluminal coronary angioplasty to 50% immediately after, and to 63% at the time of the follow-up angiogram. These changes were similar in the 2 groups (Figure 3). The changes in minimal absolute luminal diameter also were not different in the 2 groups (Figure 4). The overall patient restenosis rate was 36% in the diltiazem and 32% in the placebo groups ($p = 0.30$). Late cardiac events, including recurrent angina, death, Q-wave myocardial infarction and need for elective coronary artery bypass graft surgery during follow-up, occurred with similar frequency in the 2 groups (Table III). Laboratory values at baseline and at 1-year follow-up were similar in the 2 groups (Table IV). Recurrent angina pectoris during follow-up occurred in 46 and 37% of diltiazem- and placebo-treated patients, respectively.

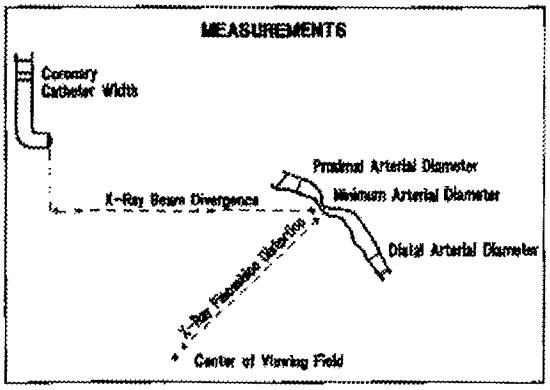

FIGURE 1. Quantitative angiographic technique uses measurements of the minimal proximal and distal arterial diameters. Catheter is used as the reference standard, allowing for accurate, absolute measurements. Corrections are made for x-ray beam divergence and pincushion distortion.

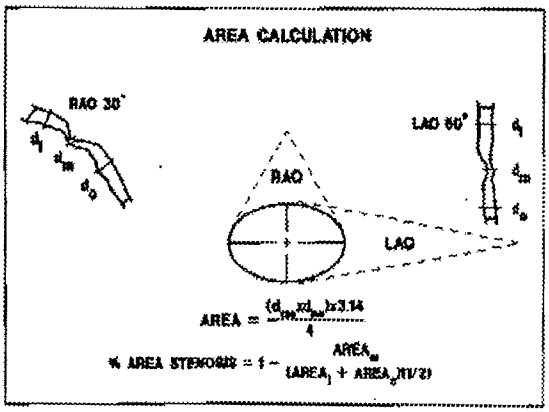

FIGURE 2. Area calculations are based on diameter measurements made in 2 orthogonal views. di = inlet diameter; dm = minimal diameter; do = outlet diameter; LAO = left anterior oblique; RAO = right anterior oblique.

TABLE II Percutaneous Transluminal Coronary Angioplasty Complications

	Treatment		
	Diltiazem (n = 102)	Placebo (n = 99)	p Value
None (%)	87 (84.5)	83 (84.5)	NS
Death (%)	1 (0.9)	1 (1.0)	NS
Q-wave AMI (%)	0	3 (3.1)	0.12
Acute occlusion (%)	5 (4.9)	5 (5.1)	NS
Emergency surgery (%)	3 (2.9)	2 (2.0)	NS
Dysrhythmia (%)	0	1 (1.0)	NS
Unstable angina (%)	1 (0.9)	2 (2.0)	NS
Intimal dissection (%)	4 (3.8)	4 (4.1)	NS
Ventricular fibrillation (%)	0	0	NS
Shock (%)	2 (1.9)	0	NS
Focal spasm	0	0	NS

AMI = acute myocardial infarction; NS = difference not significant.

TABLE III Events During Follow-Up

	Treatment		
	Diltiazem (n = 102)	Placebo (n = 99)	p Value
Death (%)	3 (3)	0	0.24
CABG (%)	1 (1)	1 (1)	1.00
Q-wave MI (%)	0	1 (1)	0.49
Angina (%)	38 (37)	39 (39)	0.46

CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

TABLE IV One-Year Laboratory Values

	Treatment		
	Diltiazem	Placebo	p Value
Total cholesterol (mg/dl)	172 ± 96	188 ± 93	0.3
HDL cholesterol (mg/dl)	24 ± 17	25 ± 15	0.7
Triglycerides (mg/dl)	125 ± 103	138 ± 100	0.4
Creatine kinase	88 ± 86	84 ± 91	0.8
Albumin (g/dl)	3 ± 2	4 ± 2	0.5
BUN/creatinine ratio	10 ± 6	10 ± 8	0.8
Total protein (g/dl)	5 ± 3	6 ± 3	0.4
Albumin/globulin ratio	1 ± 1	1 ± 1	0.6

BUN = blood urea nitrogen; HDL = high-density lipoprotein.

DISCUSSION

Aspirin and calcium antagonists have been used empirically after coronary angioplasty since Gruentzig et al[19] first introduced the procedure 13 years ago. Aspirin has stood the test of time and, although it does not prevent restenosis, it has proven highly effective in preventing acute vessel closure after coronary angioplasty.[20,21] Convincing clinical evidence to support the routine use of calcium antagonists after elective angioplasty does not exist. The results of the current study suggest that diltiazem does not prevent restenosis or recurrent cardiac events after coronary angioplasty.

Acute vessel closure: Abrupt, acute or subacute vessel reocclusion after coronary angioplasty is generally the result of intimal and medial disruption with flap formation, thrombus accumulation and coronary vasospasm. The problem of coronary vasospasm after angioplasty is probably underappreciated by many clinicians. A study using quantitative stenosis measurements with sequential angiograms in the first several hours after dilation demonstrated routine progressive coronary vasoconstriction in the dilated segment.[22] This vasospasm occurs even in patients pretreated with aspirin and calcium antagonists, which suggests that it results from a direct receptor-mediated or myogenic response to arterial injury. This reflex vasoconstriction can be reversed or prevented by nitroglycerin. Although diltiazem was ineffective in preventing acute vessel reocclusion in this series, all patients were routinely pretreated with sublingual isosorbide dinitrate and intravenous verapamil. Additionally, transcutaneous nitroglycerin was used for the first 24 to 48 hours after angioplasty. It is possible that diltiazem may be useful in preventing acute events due to abrupt vessel closure as a consequence of coronary vasospasm in patients who are not pretreated with nitrates or verapamil, although this question was not addressed in the current study.

Restenosis: Restenosis is emerging as a major focus of cardiovascular research efforts. This is a complex pathophysiologic process that involves more than one

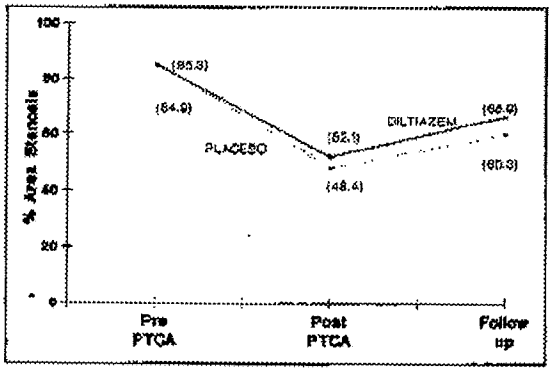

FIGURE 3. Changes in the mean area percent stenosis in the diltiazem *(solid line)* and placebo *(dotted line)* groups were similar during the study (difference not significant). PTCA = percutaneous transluminal coronary angioplasty.

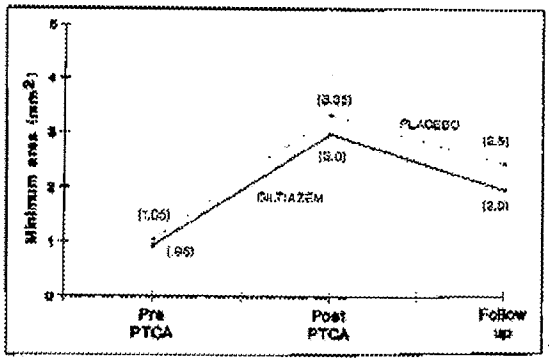

FIGURE 4. Changes in the minimal absolute area stenosis were similar in the 2 groups during the study. PTCA = percutaneous transluminal coronary angioplasty.

mechanism. Myointimal smooth muscle cell proliferation is the most common histologic picture,[23,24] although elastic recoil of the vessel wall has also been implicated as a cause of late luminal narrowing after coronary angioplasty.[2,3] It is theorized that this elastic recoil is independent of medial injury (unlike the proliferative response) and involves overstretching of the vessel. Restenosis in this scenario is the result of gradual "restitution of tone" of the overstretched segment. The results of this study, as well as previous reports,[25,26] suggest that calcium antagonists are ineffective in preventing this type of restenosis. Abnormal vasomotion in the dilated coronary segments has been observed to occur frequently for up to 6 months after angioplasty. One study documented an abnormal response to ergonovine provocation in 28% of patients.[27] Although the restenosis rate was high (50%) in patients with provocable coronary spasm, pretreatment with high-dose nifedipine did not prevent the abnormal vasomotor response.

Thus, calcium antagonists, like all pharmacologic and nonpharmacologic approaches used to date, appear ineffective in reducing the restenosis rate after coronary angioplasty in humans.

Recurrent cardiac events: Perhaps the most surprising result of this trial was the ineffectiveness of diltiazem in preventing recurrent angina or cardiac events during follow-up. No differences were noted with respect to the incidence of recurrent angina pectoris, acute myocardial infarction, coronary bypass graft surgery, or death during follow-up between patients treated with diltiazem or placebo. Diltiazem and other calcium antagonists, as well as β blockers and nitrates, can mask the clinical recurrence of angina pectoris in patients with restenosis. It is uncertain why this effect was not observed in the present trial, although it may in part relate to the use of concurrent antianginal medications in the study patients.

On the basis of previously reported trials, most cardiologists have come to the realization that calcium antagonists probably do not importantly influence the occurrence of restenosis after coronary angioplasty. However, many centers continue to use calcium antagonists routinely after angioplasty to prevent subacute and chronic events.[17] The results of this study suggest that calcium antagonists need not be routinely used unless a distinct indication (angina, hypertension, incomplete revascularization, and so forth) is present.

Study limitations: Although this was a randomized, double-blinded, placebo-controlled study using quantitative angiography, the angiographic follow-up rate was relatively low at 60%. The sample size (patient number) was too small to detect a modest ($\leq$25%) reduction in the restenosis rate, although the analysis of restenosis as a continuous variable using quantitative angiographic definitions increases the power of the study.[28] The routine use of nitrates and verapamil during the procedure probably obscured to some degree the effect of diltiazem on acute events early after angioplasty.

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